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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SNEDDEN, SHERIDAN	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 06/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/808,774	FISHER ET AL.	
	Examiner	Art Unit	
	Sheridan K Snedden	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-50* is/are pending in the application.

4a) Of the above claim(s) *4-11, 20-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,12-19 and 40-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/26/2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. This Office Action is in response to Paper filed 26 November 2003. Applicant's amendment of claim 1 is acknowledged. Applicant's addition of new claims 40-50 is acknowledged. Claims 1-3, 12-19 and 40-50 are under examination.

Withdrawal of Objections and Rejections

2. The objections and/or rejections not explicitly restated or stated below are withdrawn.

Maintained Objections and Rejections

Priority

3. Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, the provisional application upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims 17-19 of this application. No support is provided for method conditions that would control the oxidation/reduction in an anaerobic environment

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1-3, 10, and 15-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Gorovits *et al.* (J Biol Chem. 1997 Jan 3;272(1):32-5). Gorovits *et al.* teach a DHFR refolding assay in which (a) the DHFR is first presented in an unfolded state, (b) GroEL is added to form the necessary chaperonin-DHFR complex, and (c) the chaperonin-DHFR complex was exposed to urea concentrations of less than 0.5M (see Materials and Methods; regarding claims 1-3, 10, and 15-16). The co-chaperonin GroES was also added in some experiments (regarding claim 12). Thus, the reference anticipates the claimed invention.

Applicant argues that the above reference does not teach or suggest "exposing [the] chaperonin-polypeptide complex to an osmolyte." This argument has been fully considered but is not persuasive. The refolding assay of Gorovits *et al.* contains Urea at concentrations of less than 0.5M, thus, urea was necessarily present during the formation of the chaperonin-polypeptide complex in the Gorovits *et al.* assay.

Applicant further argues that the order of the process is crucial and that the complex must form prior to the exposure to the osmolyte. This argument has been fully considered but is not persuasive as the claims do not provide for such a narrow interpretation. Whereas the claims do provide an order for forming the complex, the claims do not exclude an osmolyte in any step. Gorovits *et al.* teaches the equivalent of the step in claim 1(a) where the protein is unfolded with urea. The protein is then combined with a solution that contains the chaperonin thereby allowing for the complex formation, and that then allows for the dilution of urea that would inherently promote the folding of the protein. The claims are absent any language that would distinguish the present invention from the reference.

The fact that the reference fails to teach the osmolyte urea as an agent that promotes the folding of DHFR is not relevant as this would be an inherent function of the step.

6. Claims 1-3, 10, 13-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Altamirano *et al.* (PNAS 1997 94: 3576-3578). Altamirano *et al.* teach a protein refolding assay in which (a) the protein is first presented in an unfolded state with a concentration of 8M urea, (b) then the protein is added to a gel column in which the chaperonin GroEL is immobilized in order to form the necessary chaperonin-protein complexes, and (c) the column is then washed with a refolding solution containing the osmolyte urea at concentrations of 2M (see Materials and Methods; regarding claims 1-3, 10, 14, 16). The concentration of 8M urea in the gel suspension would have been effective in reducing the aggregation of unfolding polypeptides and removal of this supernatant would have removed metastable polypeptide (regarding claim 13 and 15). Thus, the reference anticipates the claimed invention.

Applicant argues that the above reference does teach a chaperonin-protein complex that is formed prior to the addition of the osmolyte. This argument has been fully considered but is not persuasive. Urea possess the dual action of unfolding the protein at higher concentration and promoting the folding of the protein at lower concentrations. Thus, the language that requires the ordering of the steps with regards to addition of urea does not exclude its presence in the earlier steps. The claims are interpreted to require the final step of the method to include exposing the chaperonin-protein complex to concentrations of urea that would promote the

folding of the protein, this would include the dilution of urea already present in the sample. The present reference teaches the unfolding of protein in 8M urea, applied to the column where binding takes place and a washing step in the presence of 2M urea. Are requirements of the claims are established. Furthermore, is in inherent that use of the osmolyte and chaperonin together would have either a additive or synergistic in achieving a greater "promoting."

7. Claims 1-3, and 12-19 are rejected under 35 U.S.C. 102(b) as being anticipated by Altamirano *et al.* (Nat Biotechnol. 1999 Feb;17(2):187-91). Altamirano *et al.* teach a protein refolding assay in which (a) the protein Cn5 toxin is first presented in an unfolded state, (b) then the protein is mix with a refolding matrix containing the chaperonin GroEL and the co-chaperonin DsbA immobilized on PPI-agarous, and (c) the column is then washed with a refolding solution containing the osmolyte arginine and the redox agent GSH (see Materials and Methods; regarding claims 1-3, 12, 14, and 19). The assay is conducted under an inert Argon atmophere in order to control the oxidation/reduction in an anaerobic environment (see page 190, second column; regarding claims 17-18). The incubation with the GroEL agarous gels and removal of the supernatant is effective in reducing the aggregation of unfolding polypeptides and removal of this supernatant would have removed metastable polypeptide (see abstract; regarding claim 13 and 15). Altamirano *et al.* discusses the difficulty in refolding the Cn5 toxin and would have not been successfully refolded without the combination of all steps in the method (see page 187-188; regarding claim 16). Thus, the reference anticipates the claimed invention.

Applicant agrues that the osmolyte/chaperonin system is not the same as the fragmented "minichaperone system" taught by Altamirano *et al.* in that the order of the steps are different. Applicants argue that a precise order is required by the claims. This argument has been fully considered but is not persuasive. A nature order of the steps in implied by the claim language, however, there is no language in the claims that require a narrowing reading of the clams to a precise order. As the teachings of Altamirano *et al.* demonstrates, all conditions of the claims may be meet without following a precise order. Altamirano *et al.* creates an environment where once the chaperonin-protein complex is formed, the complex is immediately exposed to the osmolyte. Nothing in the claim language excludes the presence of osmolytes from earlier steps. Thus, the rejection is maintained.

New Rejections

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 12-19 and 40-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Altamirano *et al.* (Nat Biotechnol. 1999 Feb;17(2):187-91) in view of Weber *et al.* (IDS). Altamirano *et al.* teach a protein refolding assay in which (a) the protein Cn5 toxin is first presented in an unfolded state, (b) then the protein is mix with a refolding matrix containing the chaperonin GroEL and the co-chaperonin DsbA immobilized on PPI-agarous, and (c) the column

is then washed with a refolding solution containing the osmolyte arginine and the redox agent GSH (see Materials and Methods; regarding claims 1-3, 12, 14, and 19). The assay is conducted under an inert Argon atmophere in order to control the oxidation/reduction in an anaerobic environment (see page 190, second column; regarding claims 17-18). The incubation with the GroEL agarous gels and removal of the supernatant is effective in reducing the aggregation of unfolding polypeptides and removal of this supernatant would have removed metastable polypeptide (see abstract; regarding claim 13 and 15). Altamirano *et al.* discusses the difficulty in refolding the Cn5 toxin and would have not been successfully refolded without the combination of all steps in the method (see page 187-188; regarding claim 16).

Altamirano *et al.* does not teach the use of oligomeric chaperonins.

Weber *et al.* teach that the oligomeric structure of GroEL/GroES is required for the biologically significant chaperonin function in protein folding.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to use oligomeric GroEL/GroES in the method of Altamirano *et al.* The person of ordinary skill in the art would have been motivated to make the above substitution and would have expected success, because Weber *et al.* teach that the oligomer structure of the chaperonin is require in protein folding. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, *prima facie* obvious.

Conclusion

9. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan K Snedden whose telephone number is (571) 272-0959. The examiner can normally be reached on Monday - Friday, 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (571) 272-0951. The fax phone number for regular communications to the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

SKS
May 24, 2004

SKS

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER